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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,746	02/18/2004	Sheldon B. Greer	2954-128	2050

6449 7590 09/25/2008

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24,28-33 and 39-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,28-33 and 39-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/26/2008 has been entered.

Formal Matters

Applicants' response and amendments to the claims, filed 8/26/2008, are acknowledged and entered. Claim 5 has been cancelled by Applicant. Claims 22-24, 28-33, and 39-59 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claim 5 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-24, 28-31, 43-46, 49-51, and 55-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Original claim 22, as submitted in Applicant's response filed 7/10/2006, recited a method of treating a tumor "*consisting essentially of* the steps of administering an effective amount of 5-chloro-2'-deoxycitidine and an effective amount of a cytidine deaminase inhibitor to a subject, and then exposing the subject to an effective level of radiation." However, in the amendment filed 8/26/2008, Applicant amended claim 22 to recite an additional method step: "...and thereafter b. administering to said patient 5-chloro-2'-

deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue." Accordingly, claim 22 and claims dependent therefrom are unclear as to what methods steps are and are not excluded by the "consisting essentially of" language.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 22-24, 28-31, 43-46, 49-51, and 55-56 under 35 U.S.C. 112, first paragraph (New Matter), is **withdrawn** in light of Applicants' arguments.

Claims 22-24, 28-33, and 39-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 22 and 32 have been amended to recite an additional method step for which no support is found in the originally filed disclosure. Accordingly, the limitation, "...and thereafter b. administering to said patient 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue" (claim 22) and "...and thereafter b. administering to any surviving cells and the surrounding tissue 5-chloro-2'-deoxycytidine and tetrahydrouridine" (claim 32) constitute new matter.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is

whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a methods comprising three distinct steps: a) administering 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor; b) exposing the tumor to a level of radiation; and 3) *thereafter* administering to the patient 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue. The third step recited in the claims was added in the amendment filed 8/26/2008. Applicant asserts that support for this amendment is found in the specification at page 26, paragraph 4 through page 27, paragraph 2 (Applicant's Remarks, page 3, first paragraph). The language at page 26, paragraph 4 through page 27, paragraph 2 of the originally filed disclosure is repeated in its entirety below.

> The importance and novelty of this approach is that it more reasonably assures a tumor cure without damage to underlying tissue. Instead of using a high dose of radiation, which could affect normal tissue (in spite of the great selectivity of the radiosensitizer of this invention), the present invention involves an independent strategy or approach vs the remaining cells of the tumor which may have escaped the lethal effects of radiation. CldC itself and the nucleoside analogs make CldC a more effective radiosensitizer because they may have the dual role of affecting gene expression in surviving tumor cells by virtue of its inhibition of 5-methylcytosine DNA transferase. This will more effectively assure complete tumor control, or at least prevent tumor progression and metastasis, by A) restoring the tumor cells to a normal state by reactivating tumor suppressor genes and B) restoring genetic stability to the surviving cells by 1) reactivating the transcription of mRNA encoded genes whose protein products prevent further DNA modification (additional alterations in DNA could lead to further progression towards neoplasia, 2) reactivating the expression of enzymes which repair alterations in the DNA: of the surviving cells, or, more directly, 3) preventing the epigenetic inheritance, via maintenance methylation, of hot spots of mutation in the DNA of the surviving cells.
>
> XV. The present invention allows a method of treatment in which the tumor is irradiated prior to drug treatment to induce greater deoxycytidine kinase (dCK) activity in the target cells. Deoxycytidine kinase initially converts CldC, FdC and 4-N-methylamino FdC to their anabolites, CldCMP, FdCMP, and 4-N-methyllamino FdCMP, respectively.

The Examiner fails to see where in the cited passage support for an additional method step of administering to the patient 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue *after* initial administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by radiation is found. While Applicant

discloses that CldC itself and the nucleoside analogs make CldC a more effective radiosensitizer because they may have the dual role of affecting gene expression in surviving tumor cells by virtue of its inhibition of 5-methylcytosine DNA transferase, nowhere does Applicant disclose that CldC and nucleoside analogues are intended to be administered *after* radiation treatment to treat surviving tumor cells in the surrounding tissue.

It is clear from Applicant's disclosure that he did not envision administering 5-chloro-2'-deoxycytidine and tetrahydrouridine *after* radiation therapy. For example, at page 29, fourth paragraph to page 30, first paragraph, Applicant states that, "The agents of the present invention can be administered one to four times a day. The treatment with the agents of the present invention can be repeated daily or temporarily stopped for up to several days during the course of the treatment of the tumor. The irradiation can begin after the first administration of CldC. Alternatively, the irradiation can begin after an interval of about 4 hours to about 18 hours, preferably about 6 to 14 hours, after the last administration of CldC." Also see Table 1, wherein in no instance are 5-chloro-2'-deoxycytidine and tetrahydrouridine administered after radiation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-24, 28-29, 32, 39, 42-44 and 47 are again rejected under 35 U.S.C. § 102(b) as being anticipated by **Greer** (WO 85/01871; Published May 9, 1985).

Instant claim 22 recites a method of "achieving tumor control and improved irradiation efficacy" comprising three steps. First, a patient is administered CldC and tetrahydrouridine (H_4U) in amounts effective to produce elevated levels of CldUMP and CldU in a tumor. Second, the patient is exposed to an effective level of radiation delay the growth of said tumor. Third, the patient is "thereafter" administered 5-chloro-2'-deoxycitadine and tetrahydrouridine.

Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U)

(Abstract). Further, Greer teaches that when CldC is administered with H_4U, CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 16-28). The reference thus explicitly teaches step one of the instant claims. Also see Table 1 at page 41 of Greer, wherein on days WED and THURS, CldC and H_4U are administered prior to radiation.

The invention of Greer provides therapeutic materials and procedures for treating solid tumors using X-ray or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-15). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is preferably administered with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy.

The slow release formulations of Greer anticipate the limitations of instant claim 24. Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds. Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference, it is clear that Greer also unequivocally teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14). While such therapy may be *enhanced* by co-administration with an inhibitor of pyrimidine biosynthesis, the fact remains that 5-chloro-2'-deoxycytidine and tetrahydrouridine are alone effective to sensitize tumors to radiation when administered without such an inhibitor of pyrimidine biosynthesis.

The instantly claimed methods only require that a tumor be sensitized to radiation when a patient is administered 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by an effective

level of radiation. Table 1 of Greer (page 41) explicitly teaches administering to a patient CldC + H4U followed by radiation wherein none of PALA, FdC, 4-N-methyl FdC, and FdU are administered to the patient (days WED and THURS of the "Standard Protocol" in Table 1). Also note that following the radiation on WED at 3:00 pm, CldC + H4U are administered to the patient on THURS at 9:00 am, thus teachings the limitations "...and thereafter b. administering to said patient 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue" (claim 22) and "...and thereafter b. administering to any surviving cells and the surrounding tissue 5-chloro-2'-deoxycytidine and tetrahydrouridine" (claim 32).

It is clear from the Greer reference that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine is effective to sensitize tumors to irradiation. As such, Greer clearly anticipates the claimed method of treating tumors comprising sensitizing tumors to radiation by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine and exposing a patient to an effective level of radiation.

Applicant's arguments have been carefully considered but they are not persuasive. Applicant argues (Remarks, page 3, first paragraph):

> Greer does not anticipate these newly amended claims because Greer does not teach any post-radiation treatment for tissue surrounding a tumor, nor for tumor cells that survive radiation treatment. In addition, it would not be inherent that a radiation treatment protocol would be followed by an additional drug treatment protocol.

However, as discussed *supra*, in Table 1 of Greer (page 41), the "Standard Protocol" teaches that on days WED and THURS, CldC and H4U are administered to the patient, without PALA, FdC, 4-N-methyl FdC, or FdU, and then radiation is administered. Further, following the radiation on WED at 3:00 pm, CldC + H4U are administered to the patient on THURS at 9:00 am, thus teachings the limitations "...and *thereafter* b. administering to said patient 5-chloro-2'-deoxycytidine and tetrahydrouridine in amounts effective to treat any surviving tumor cells in the surrounding tissue" (claim 22) and "...and *thereafter* b. administering to any surviving cells and the surrounding tissue 5-chloro-2'-deoxycytidine and tetrahydrouridine" (claim 32). Greer thus teaches the claimed methods as recited in independent claims 22 and 32.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 30-31 and 40-41 are again rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985) in view of **Shepherd *et al.*** (Cancer, 1992, vol. 70, pages 2250-2254, Abstract).

Greer teaches as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the use of yttrium-90 as a radiation source.

However, Shepherd *et al.* disclose that yttrium-90 microspheres have been used in the treatment of primary hepatocellular carcinoma (Abstract).

Thus, the instantly claimed methods wherein the radiation source comprises yttrium 90 needles would have been *prima facie* obvious in view of Shepherd *et al.* who teach that yttrium-90 is a radiation source used in the treatment of cancer. The skilled artisan would be imbued with at least a reasonable expectation that yttrium-90 would be a viable source of radiation in the treatment methods of Greer. The motivation to use other radiation sources is clearly found in Greer, who teaches that radiation can be from "other radiation sources", aside from those explicitly disclosed (page 2, lines 10-15).

Claims 33, 45-46, 48, 50-51, 53-56 and 58-59 are rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985).

Greer teaches as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not explicitly teach the treatment of the specific tumors (*e.g.*, lung, prostate, breast, etc.) recited in the instant claims. The reference also does not explicitly teach the treatment of tumors resulting from gene silencing.

However, given the broad teachings of Greer as discussed *supra*, the skilled artisan would reasonably expect that the methods of sensitizing tumors to irradiation as taught in Greer could be predictably used to treat tumors of different organs. It is recognized in the art that radiation therapy is a useful, predictable treatment of tumors of different origin and etiology. As such, the

skilled artisan could readily apply the methods of Greer to patients having tumors in different organs or arising from a different natural or environmental cause.

Claims 49, 52 and 57 are rejected under 35 U.S.C. § 103(a) as being obvious over **Greer** (WO 85/01871; Published May 9, 1985) in view of **Nagatake *et al.*** (Cancer Research, 1996, vol. 56, pages 1886-1891).

Greer teaches as applied to claims 22-24, 28-29, 32, 39, 42-44 and 47, *supra*. Greer does not teach the treatment of a tumor associated with hypermethylation.

However, Nagatake *et al.* disclose that hypermethylation of DNA is recognized as a consistent molecular change in human cancers, including lung cancer (page 1886, left column, first paragraph).

Thus, the instantly claimed methods of treating tumors associated with hypermethylation of nucleic acids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Greer discloses a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract). Nakatake *et al.* disclose that altered DNA methylation may play a role in the oncogenesis of human neoplasms, including lung cancer. The skilled artisan would be imbued with at least a reasonable expectation that the methods disclosed in Greer could be used to treat tumors associated with hypermethylation of nucleic acids because the Greer reference is clearly not limited to the treatment of any particular tumor of specific etiology. Further, the skilled artisan could predictably use irradiation to treat any tumor regardless of etiology. Such methods of treating tumors with irradiation are commonplace in the art of treating cancer.

Applicant's arguments with respect to the above 35 U.S.C. 103 rejections have been carefully considered but they are not persuasive. Applicant argues (Remarks, page 4, paragraph 2):

> Independent claims 22 and 32 have been amended as discussed above. Neither the Shepherd reference nor the Nagatake reference discloses the step of

> additional drug treatment following radiation treatment and thus they cannot render the subject claims obvious over Greer. In addition, it would not be obvious to one of skill in the art to treat post-radiation surviving tumor cells with a drug combination that is known in the art as only a radiation-sensitizer.

Applicant continues (Remarks, paragraph bridging pages 4 and 5):

> Furthermore, Applicant would like to point out that tetrahydrouridine inhibits the cytidine deaminase of normal cells to a greater extent than the cytidine deaminase of tumor cells - thereby selectively protecting the normal cells from the formation of the radiosensitizing and cytotoxic deaminated derivative. Thus, the claimed drug treatment not only sensitizes tumor cells to radiation treatment, but also improves the biochemical profile of both surviving tumor cells and surrounding tissue cells in such a manner as to improve the overall outcome for the patient. It would not have been obvious to one of skill in the art that the claimed drug combination would have this paradoxical effect; that is, that it would increase the likelihood that tumor cells would die following radiation exposure, while also increasing the likelihood that cells that didn't die would have a more advantageous biochemical profile following treatment.

With regard to Applicant's argument that Shepherd and Nagatake do not disclose the step of additional drug treatment following radiation treatment, this issue has been addressed in the discussion supra with respect to the 35 U.S.C. 102 rejection over Greer. With regard to Applicant's argument that it would not have been obvious to one of skill in the art that the claimed drug combination would have this [the claimed drug treatment not only sensitizes tumor cells to radiation treatment, but also improves the biochemical profile of both surviving tumor cells and surrounding tissue cells in such a manner as to improve the overall outcome for the patient] paradoxical effect, such a characterization of the effects of the treatment regimen taught, suggested, and motivated by the Greer reference in combination with the cited references is not a patentable distinction over the prior art. In other words, carrying out the Standard Protocol taught in Table 1 of Greer would be expected to have the same effects as those claimed because the same treatment protocol is administered on days WED and THURS of Greer as that recited in the instant claims. It is noted that the instant claims do not require that PALA, FdC, 4-N-methyl FdC, or FdU are never administered to the patient, only that in the claimed method steps they are not administered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
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